PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Increased risk of COVID-19 related admissions in active solid organ cancer patients in the West Midlands region of the United Kingdom: A Retrospective cohort study
AUTHORS	Akingboye, Akinfemi; Mahmood, Fahad; Amiruddin, Nabeel; Reay, Michael; Nightingale, Peter; Ogunwobi, Olorunseun

VERSION 1 – REVIEW

REVIEWER	Ali Gholamrezanezhad USC Keck School of Medicine, Radiology
REVIEW RETURNED	22-Aug-2021

GENERAL COMMENTS	I had the pleasure to review the manuscript entitled “Increased risk of COVID-19 related admissions in cancer patients in the West Midlands region of the United Kingdom: A Retrospective cohort study”. Unfortunately I found the methodology of the study suboptimal. A significant number of important variables are not included in this study. The type of treatment, duration of cancer, the period between the last chemotherapy and infection with COVID-19, the type and stage of the underlying cancer, the radiologic extent of the disease and lung involvement, extent of extrapulmonary disease, etc, are among the important missing variables neglected in this study. I am not sure if the authors are able to re-analyze the data and reconduct the study to include these variables.

REVIEWER	Ankit Madan SOVAH Cancer Center
REVIEW RETURNED	25-Sep-2021

GENERAL COMMENTS	1.Methods- why were patients with non-solid organ cancers excluded? Since only solid tumors were included, this should be reflected in abstract and title; ‘Active cancer ’ will be interpreted as all cancers-solid organ and hematological malignancies and data may be extrapolated for all tumors. 2.Is less than 40% missing data standard of care for machine learning algorithm? 3.Results; Catchment area included 426,658 people. 22,279 had active cancer. When calculating non-cancer patients getting covid-19 getting hospitalized the calculation should look like 526/404379 [Number of non-cancer patients getting covid is 426658-22279=404379]. 4.Table 1-differences between cancer and non-cancer patients. The CRP and WBC values are similar in both groups, but this finding is not statistically significant. Authors should mention statistical significance in the manuscript paragraph. 5.While several studies have shown increased risk of hospitalization and ICU admission in cancer patients with COVID-19 infection and

	this does have an impact on how we need to deliver safe care. Authors also need to report on studies which have shown no increased risk from recent treatments (Lee LYW et al Lancet. 2020;395:1919-1926 ,Mehta V et al Cancer Discov. 2020). Can "recent cancer treatment" be analyzed as a variable in univariate or multivariate analysis from your data? If yes, it can add to addressing how we can deliver safe care to cancer patients. Authors have mentioned not delaying therapy due to covid-19 as it is not supported by data. 6. Kindly elaborate "ITU" abbreviation in discussion section. 7.Standard English grammatical recommendations: -Strength and limitation section: 4th point COVID-19 is spelled as COVD-19(minor typo)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ali Gholamrezanezhad, USC Keck School of Medicine
Comments to the Author:
I had the pleasure to review the manuscript entitled "Increased risk of COVID-19 related admissions in cancer patients in the West Midlands region of the United Kingdom: A Retrospective cohort study". Unfortunately I found the methodology of the study suboptimal. A significant number of important variables are not included in this study. The type of treatment, duration of cancer, the period between the last chemotherapy and infection with COVID-19, the type and stage of the underlying cancer, the radiologic extent of the disease and lung involvement, extent of extrapulmonary disease, etc, are among the important missing variables neglected in this study. I am not sure if the authors are able to re-analyze the data and reconduct the study to include these variables.

This is very specific detailed data that we unfortunately were not able to collect. All patients in the study had active cancer and were on various stages of treatment for this and we have included a figure detailing which type of cancer our cohort of patients had (Figure 1). We agree that including these variables could lead to additional variables of interest being identified with the machine learning algorithm. However, this does not detract from the proof-of-concept that the study provides in the utility of MLA in identifying risk in COVID-19 patients with a background of active cancer.

Reviewer: 2
Dr. Ankit Madan, SOVAH Cancer Center
Comments to the Author:
1.Methods- why were patients with non-solid organ cancers excluded? Since only solid tumors were included, this should be reflected in abstract and title; 'Active cancer ' will be interpreted as all cancers-solid organ and hematological malignancies and data may be extrapolated for all tumors.

This is an acknowledged limitation of our study. We had limited data on haematological malignancies and this would have distorted our analysis. As such we have focused on solid organ malignancies to provide proof of concept for our MLA. We have updated the title to reflect the scope of our study.

2.Is less than 40% missing data standard of care for machine learning algorithm?
The decision to limit the proportion of missing data to 40% was an arbitrary one, based on a compromise between a limit high enough to enable the inclusion of as many available variables as possible and low enough to enable the use of more data to predict imputable missing values with the k-nearest neighbours' algorithm.

3.Results; Catchment area included 426,658 people. 22,279 had active cancer. When calculating non-cancer patients getting covid-19 getting hospitalized the calculation should look like 526/404379 [Number of non-cancer patients getting covid is 426658-22279=404379].

We have redone the chi-squared test, substituting the value of non-cancer patients not hospitalised with COVID-19 with 404379 in place of 426658. This yields a p-value of <2.2e-16 ie there is an association between having cancer and hospitalisation with COVID-19. We summarize this in Table 2. The remaining results have been updated with the correct figures.

4.Table 1-differences between cancer and non-cancer patients. The CRP and WBC values are similar in both groups, but this finding is not statistically significant. Authors should mention statistical significance in the manuscript paragraph.

This has been updated in the relevant paragraph.

5.While several studies have shown increased risk of hospitalization and ICU admission in cancer patients with COVID-19 infection and this does have an impact on how we need to deliver safe care. Authors also need to report on studies which have shown no increased risk from recent treatments (Lee LYW et al Lancet. 2020;395:1919-1926 ,Mehta V et al Cancer Discov. 2020).
Can “recent cancer treatment” be analyzed as a variable in univariate or multivariate analysis from your data? If yes, it can add to addressing how we can deliver safe care to cancer patients.
Authors have mentioned not delaying therapy due to covid-19 as it is not supported by data.

We have updated the discussions with the relevant points made in both the above references. Mehta et al in fact mentions increased mortality in cancer patients who have COVID-19 from his cohort of 218 patients. We have added additional references in the discussion of this point from data that was published after out submission. All patients included in the study had active cancer, the patient in remission were not included , hence there is no group available for comparison.

6. Kindly elaborate “ITU” abbreviation in discussion section. We have done so by removing reference to ITU and replacing this with intensive therapy unit.

7.Standard English grammatical recommendations:
-Strength and limitation section: 4th point COVID-19 is spelled as COVD-19(minor typo)

Corrected.

VERSION 2 – REVIEW

REVIEWER	Ankit Madan SOVAH Cancer Center
REVIEW RETURNED	19-Nov-2021

GENERAL COMMENTS	Author(s) have made the required changes based on comments from last peer review submission. Decision: Accept